*A review of the important adverse biological effects of atmospheric photochemical smog on man and animals expressed in terms of atmospheric "total oxidant" concentrations is presented, based on published reports and some yet unpublished reports and research findings. Additionally, data based on laboratory exposures of man and animals to the pure agents, ozone and peroxyacyl nitrates (PAN compounds), important components of the "total oxidant" mixture which have been identified in photochemical smog, are reviewed.*

# THE BIOLOGICAL EFFECTS OF PHOTOCHEMICAL AIR POLLUTANTS ON MAN AND ANIMALS

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AIR pollution, the unfavorable alteration of one of our most important natural resources—the air we breathe—consists of emissions of gaseous and particulate products often followed by secondary reactions in the atmosphere. Except for natural causes, polluted air is a result of man's activities: industrialization, urbanization, transportation, heating of homes and buildings, and burning of wastes.

While the increasing pollution of our limited air supply has become a matter of national concern, the problem is far from new. For example, an important type of air pollution has existed and been a problem for hundreds of years. From the beginning of the 14th century to the early part of the 20th century, air pollution by coal smoke and gases has been the predominant form, and in many industrialized communities and areas of the world still is the principal form of air pollution.[1] This type of air pollution, where smoke, particulates of various sizes, and gases, primarily sulfur oxides, are produced from the combustion of coal or other fossil fuels, is characterized by its chemically reducing action and is often identified as "London-type smog." The "London-type smog" is the dominant kind of atmospheric pollution found in such large urban industrialized communities as New York, Philadelphia, and Chicago, and foreign urban communities where coal and other fossil fuels are consumed.

Another major type of community air pollution is photochemical air pollution, often called photochemical smog. This type of pollution is formed as a result of atmospheric reactions initiated by ultraviolet radiation from sunlight on certain gaseous emissions, the oxides of nitrogen and reactive organic compounds, derived from the combustion of organic fuels. The motor vehicle is a principal source of these emissions.[2,24] Other sources are fuel burning for heat and power, refuse burning, evaporation losses

from petroleum products, and the industrial and commercial use of organic solvents.[2]

Photochemical air pollution is of recent origin, historically speaking. The first manifestations of this form of community air pollution: excessive cracking of rubber products,[4,5,10,15] a peculiar form of leaf injury to many agricultural and ornamental crops,[3,5-11] and eye irritation,[5,10-12,15] were noted in the Los Angeles area only a little more than 20 years ago, hence the commonly used designation, "Los Angeles-type smog." Other expressions of photochemical smog are respiratory distress,[13,14,54] haze formation causing a reduction in visibility with consequent hazards to ground, air, and water transportation,[10-12,15-17,24] and a characteristic objectionable odor,[17] as well as the presence of unusually high levels of atmospheric photochemical oxidants. More recent findings of effects on man and animals will be described in some detail below.

The photochemical oxidants are a major class of gaseous compounds found in photochemical smog. They consist of a complex mixture of atmospheric oxidizing substances which vary in composition with time and place; all the components are not yet completely defined chemically. Nonetheless, they can, with appropriate analytical procedures, be measured routinely and analyzed collectively as "total oxidant," which serves as a useful index of photochemical air pollution. The rate of formation of photochemical oxidants is controlled by the intensity of sunlight, and the concentrations of the major reactant gases—the reactive organic compounds (olefins, aromatic hydrocarbons, and aldehydes) and nitrogen oxides.[15,19,20] The accumulation of these reactant gases, in turn, is determined by their emission rates from the several sources, as well as by meteorological and topographical factors. Meteorological factors, such as low wind speed and vertical stability, play an important part in the accumulation of photochemical air pollutants in the community air.[21] Temperature plays a significant but secondary role in the rate of accumulation of photochemical air pollutants: all chemical reactions are accelerated with increased temperature.[18,19]

The adverse effects of photochemical smog now occur in every region of the United States. Higher community photochemical oxidant concentrations and greater frequency of other photochemical smog manifestations, however, in general are found more frequently in the lower latitudes where ample sunshine and higher temperatures prevail year round.[21]

An "oxidant," as used in the air pollution field, may be defined as a substance which oxidizes a selected reagent under specified conditions. Currently, the field methods commonly used for routine measuring of the ambient photochemical oxidants in the community atmosphere measure "total oxidant," i.e., the collective net oxidizing effect of all the oxidizing substances formed in the atmosphere, indiscriminately. Oxidant values, measured as "total oxidant" usually by the neutral potassium iodide method, serve as practical indexes of the various biological and material expressions of photochemical smog, i.e., when the "total oxidant" level is high the various signs and symptoms associated with photochemical smog are more pronounced; when the "total oxidant" level is low, the associated manifestations of photochemical smog are minimal.

Using more sophisticated instrumentation, however, some of the individual atmospheric photochemical oxidants have been determined. Ozone has been identified as a principal oxidant produced in photochemical smog.[4,5,15,17-20,22,23] Other atmospheric oxidants which have been isolated and identified are peroxyacyl nitrates, a related group of organic peroxidic nitrogen compounds,[25-28] designated as PAN compounds, or more recently as PaNs.[29] The PaNs have been determined

by Stephens and his associates to be a homologous series of compounds; they have identified peroxyacetyl nitrate (PAN), the principal compound in the group, as well as peroxyproprionyl nitrate (PPN), and peroxybutyryl nitrate (PBN), thus far.[25-28] Other oxidants present in photochemical smog are nitrogen oxides, which act as weak oxidants, other organic peroxides, free radicals, and other compounds yet unidentified.

Daily fluctuation of "total oxidant" is a major characteristic of photochemical smog and follows a distinctive pattern: low concentrations at night are followed by an increase in the early morning; a peak reached during the remainder of the sunlit hours, usually in the afternoon, is followed by slow decay and a gradual disappearance after sunset.[12,17,30,31] At peak levels of "total oxidant," ozone may constitute up to 90 per cent or more of this total (neutral KI methods).[32,33] An annual cycle exists; high hourly concentrations are found more frequently, usually from May through October, than during the rest of the year.[30,34] Peak "total oxidant" levels up to about 1.0 ppm in dense community photochemical smog have been reported.[35]

Some of the more recent studies and findings on the effects of atmospheric photochemical oxidants expressed in terms of "total oxidant" levels (neutral KI method) will be briefly described. Data on the effects of ozone and PAN based on laboratory or chamber exposures of humans and of animals to the generated pure agents are also included because of their identification as important oxidants found in photochemical smog. The data based on exposures to the single oxidizing agents in pure form are supplementary to the data based on ambient air studies expressed as "total oxidant." An understanding of their effects contributes substantially to our knowledge of the effects of the "total oxidant" mixture.

Substantial data on the adverse effects of generated ozone on man and animals are available. Ozone has been recognized as an important industrial toxicant for a long time, much before an awareness of its presence as an important component in photochemical smog was identified. It is formed in nature by high voltage discharge during thunderstorms and is formed in natural processes by the photodissociative action of solar ultraviolet short wavelength radiation on the oxygen molecules in the lower stratosphere.[36,37] It has been encountered occupationally in appreciable levels in inert gas shielded arc-welding devices[38-42]; and it is formed by high voltage discharge from the brushes of motors, neon signs, and other electrical equipment. It has been used in the past and to a limited extent at present for air purification and odor control in buildings and homes by generation from ozonizing equipment[43-47]; in cold storage plants for the control of molds and bacteria[48]; and in the treatment of sewage wastes,[49] and purification of drinking water.[50] On the other hand, the PaNs have neither been found in nature nor been identified as contaminants in other areas of environmental health excepting air pollution. In addition, their synthesis and generation for purposes of laboratory studies and their methods of measurement are much more difficult than those for ozone; hence, comparatively little is known about them at present.

## Effects of Photochemical Smog on Man

### *Short-Term Effects*

#### Eye Irritation

The most commonly experienced and recognized attribute of photochemical smog by man is eye irritation. The components causing eye irritation have not been completely identified as yet but there is a significant correlation between eye irritation and levels of atmospheric "total oxidant" based on eye irritation surveys.[75,76] Eye irritation is experienced

at community oxidant levels of 0.10 ppm and higher by substantial elements of the population.[51] To a high degree, eye irritation is subjective; it is influenced by abundance of light, humidity, haze, and wind currents, as well as the somatic condition of the observer.[24]

#### Odor

There is a characteristic pungent odor associated with photochemical smog.[5,52] Ozone is an acrid component of this odor.[17,52]

### *Prolonged Effects*

#### Respiratory Effects

Recent studies have shown that it is harder for humans, especially patients suffering from chronic respiratory disease, to breathe in areas having even a moderate level of photochemical air pollution.[13,54,78] Patients with chronic bronchopulmonary disease, when exposed in clinical studies to smoggy Los Angeles air having 0.138 ppm "total oxidant" (average of the daily maxima) for one week, showed a significant and uniform increase in oxygen consumption and a decrease in arterial blood oxygen tension (oxygen partial pressure) during light exercise compared with the findings in each patient while breathing clean filtered air for a similar period.[13,54] Thus, although the patients were consuming more oxygen, less of it was being made available to the body. These patients also had greater difficulty in breathing (increased pulmonary airway resistance and work of breathing) when breathing the smoggy air.[13,54]

## Effects of Photochemical Smog on Animals

### *Short-Term Effects*

Studies on guinea pigs exposed over their lifetime to atmospheric photochemical smog showed that the animals experienced greater difficulty in breathing on days of high photochemical air pollution levels (0.30 ppm "total oxidant" and above for three hours).[55] Even more significant increases in breathing resistance, particularly in the older animals, occurred on days having severe smog (0.50 ppm peak "total oxidant" levels and above,[56] the first alert level in Los Angeles).[11] Temporary ultrastructural alterations in the wall cells of lung alveoli of nine-month-old mice occurred after exposure to a severe smog episode (>0.40 ppm "total oxidant" for 2-3 hours).[79] Recovery of the alveolar tissues took place within 14 hours.[79] Laboratory mice exposed to a diluted irradiated auto exhaust atmosphere containing as low as 0.15 ppm mean "total oxidant" for four hours and then to an infectious Streptococcus aerosol showed a significant increase (enhancement) of mortality (27 per cent) over similarly infected control animals exposed first to filtered air.[77]

### *Prolonged Effects*

Laboratory mice (A and A/J strains) exposed to community photochemical smog levels (0.14 ppm average of the daily "total oxidant" maxima) over a 16-month period showed an increase in lung tumor development (adenoma) in the aging animals when compared to controls exposed to filtered air.[57]

Several strains of young laboratory mice, five to eight weeks old, exposed continuously to low levels of synthetic smog (0.08 ppm average of the "total oxidant" daily maxima, irradiated auto exhaust cycled within test chambers to simulate the daily oxidant fluctuation pattern occurring in the atmosphere) showed increased susceptibility to pulmonary infection and chronic disease during the latter half of the animals' lifetime compared to controls exposed only to clean filtered air.[58] Significant de-

creases in mouse fertility and survival rate of infant $LAF_1$ strain mice were also manifested during the 13-month exposure period (through the animals' effective reproductive period).[58]

## Effects of Ozone on Man

### *Short-Term Effects*

#### Odor

The characteristic sharp odor of ozone, sometimes described as an "electrical" odor, can be detected instantaneously at very low concentrations (<0.02-0.05 ppm), depending on individual acuity.[53,59-60,44] At somewhat higher concentrations (0.05-0.10 ppm) the odor becomes more pronounced and disagreeable.[53,60]

#### Respiratory Effects

Ozone is a severe irritant to all mucous membranes. Significant exposures may cause pulmonary congestion and other complications. The first symptoms of irritation due to ozone, dryness of the upper respiratory passages and initial irritation to the mucous membranes of the nose and throat occur after brief exposures (13-30 minutes) to low concentrations (0.05-0.10 ppm).[53,44] At higher concentrations (0.30-1.0 ppm) all within the range of community oxidant levels and exposures for longer intervals (15 minutes-2 hours), marked respiratory irritation is accompanied by respiratory distress (choking, coughing and severe fatigue) particularly so at the upper end of this range.[53,61-63]

At relatively high concentrations, equivalent to the ozone content in severe photochemical smog, lung function is impaired for the duration of exposure and for some time after. Normal subjects exposed to a range of 0.6-0.8 ppm ozone in single two-hour periods showed a marked change in lung function (highly significant reduction in diffusing capacity (25 per cent) and significant reduction in vital capacity and forced expiratory volume) lasting up to 24 hours.[41] The subjects developed bronchial irritation and substernal soreness lasting up to 12 hours, as well as a slight dry cough disappearing within 24 hours. At still higher concentrations, beyond the maximum levels presently found in community photochemical smog (1.5-2.0 ppm), a single two-hour exposure to ozone caused general morbidity in a man lasting for approximately two weeks.[64] His immediate symptoms included impaired lung function, severe chest pains, altered taste sensation, coughing, headache, and extreme fatigue. During the period of severe malaise following exposure, the subject also showed a loss of coordinating ability and difficulty in expression and articulation.[64]

#### Effects on Vision

Humans when exposed to ozone concentrations as low as 0.20 ppm (0.20-0.50 ppm) for three hours showed a considerable decrease in visual acuity and changes in the extra-ocular muscle balance, reduced night vision, lateral phoria (divergence), and other changes in visual parameters.[65] These effects were all manifested at concentrations of 0.20 in three hours; effects were more pronounced at 0.35 and 0.50 ppm respectively.

### *Prolonged Effects*

Few prolonged ozone exposure studies of humans have been reported. Occupational exposures of welders to intermittent relatively high concentrations of ozone (range of 0.3-1.7 ppm) over a two-week period caused severe recurrent headache, fatigue, chest pains, difficulty in breathing and wheezing.[40,66]

## Effects of Ozone on Animals

Ozone is a strong irritant of the mucous membranes of animals. It augments

the morbidity effects of respiratory infection (and shortens the morbidity span) in test animals exposed both to the respiratory infection and to ozone. Recent findings indicate that ozone also may produce secondary systemic effects on body metabolism and function, including the inhibition of normal thyroid function.[67]

*Short-Term Effects*

A mean ozone concentration as low as 0.08 ppm for three hours caused a significant increase in mortality of Streptococcus-infected test animals over similarly infected animals not exposed to ozone.[68] In a recent study on the enhancement of respiratory disease due to prior exposure to ozone, Coffin exposed groups of Swiss mice each weighing 25 g. to a specific level of ozone for three hours followed by exposure for half an hour to an aerosolized culture of Streptococcus in a series of ozone levels ranging from 0.05 to 0.50 ppm. The control animals were exposed for three hours to filtered air and then to the Streptococcus aerosol for half an hour. Mortality was measured over a ten-day period. The increase in mortality after exposure to 0.08 ppm ozone for three hours and then the Streptococcus aerosol was 23 per cent over the mortality of the controls. ($P$ value $<0.05$.)

Concentrations of ozone comparable to commonly found atmospheric community pollution levels also caused a decreased activity in mice (decreased running ability after exposure to 0.20 ppm for 6 hours), while ozone levels of 0.34 ppm and above for two hours caused temporarily impaired lung function.[69] At ozone concentrations well above present community levels (1.50 ppm and above), pathological lung changes occurred in previously healthy mice after a single four-hour exposure which apparently were reversible after withdrawal from the ozone environment.[70]

*Prolonged Effects*

Continuous ozone exposure for 3-17 weeks at concentrations of 0.10-0.25 ppm shortened the lives of infected guinea pigs and increased their mortality rate,[71] while intermittent prolonged exposures (0.10-0.20 ppm for seven hours/day, five days/week for three weeks) caused an increase in the mortality of newborn mice.[72] Significant increased mortality and severe chronic lung injury including hemorrhage, fibrosis of the lung parenchyma and constriction of the lung airways occurred in guinea pigs and rats when intermittently exposed to ozone concentrations of 1.50 ppm (neutral KI method) for 62 weeks.[73]

## Effects of PAN (Peroxyacetyl Nitrate) and PAN Compounds (Peroxyacyl Nitrates) on Man and Animals

Since the PAN compounds have been used in human or animal exposures for only a short time, comparatively little information has been developed to date.

## Effects of PAN or PAN Compounds on Man

Peroxyacetyl nitrate (PAN) appears to have an effect on pulmonary function of humans similar to that reported for ambient oxidant. In a recent study, healthy students when performing moderate exercise and breathing 0.30 ppm PAN for five minutes showed a statistically significant increase in oxygen uptake over the oxygen consumption of the same students during an identical period when breathing clean filtered air during exercise; breathing (expiration velocity during the recovery stage) was also affected.[74]

PAN has been reported to cause eye irritation when panels of human volunteers were exposed to pure synthetic PAN at a concentration of 1.0 ppm for 10-15 minutes; the threshold level of

detection of synthetic PAN as an eye irritant was 0.5 ppm for 12 minutes.[26] For some reason not completely clear, the levels of PAN and other known or suspected lachrymatory agents found in photochemical smog, when tested in pure form, require a higher concentration to produce eye irritation than the concentrations of these reactants found in ambient photochemical smog.[15,75]

## Effects of PAN on Animals

No apparent evidence of pronounced injury to animals exposed to PAN in concentrations approximating atmospheric levels has been observed to date. These studies are continuing.

## Conclusion

When concentrations of photochemical oxidants are used as measures of photochemical smog intensity, a number of specific biological effects on man and animals based on both atmospheric and laboratory studies have been documented. Photochemical oxidants, such as frequently found in urban community atmospheres as measured by continuous air monitoring instruments operated by federal, state, and local agencies, cause a repeated and continuing biological impact on man and animals of varying degree and frequency in every region of the country.

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## In England Now

### A Running Commentary by Peripatetic Correspondents

Henry Sigerist, whose *Autobiographical Writings* has now appeared in an English edition, to the end of his life, never ceased to find inspiration from the sight of a blank page of his specially bound exercise books. His fountain-pen flowed, and the number of pages he set himself to write each day were covered with his characteristic widely spaced sprawling words. The lesson seems to be not to wait on inspiration. In this way one can perhaps ensure quantity. But quality? There lies the rub. Sigerist had no difficulty. To describe him as the "universal man" of the Renaissance is almost a cliché. For him there was no dichotomy between art and science. Indeed, if you wanted to sum up his lifework in a sentence, he placed medical history squarely in the framework of history as a whole. But history as a whole meant for him the everyday life of slaves, peasants, craftsmen, and labourers as well as the life of doctors, men of science, painters, musicians, architects, scholars, princes, and politicians. So that when he spoke about William Harvey his account of the contemporary scene seemed to make it inevitable that Harvey *had* to discover just as that time how the circulation worked. You might say that, like his fellow-countryman, the art historian Burckhardt, he contrived to make historical harmony out of seemingly unrelated and discordant historical figures and events.

When he came to our university in 1939 to give some guest lectures, people expected to be bored and instead were enchanted. His first lecture drew an audience of about twenty; his fifth had to be given in the largest hall and transmitted by loudspeaker to the next largest. I never saw him again. But contact with him sent me scurrying to books on the history of painting, music, and architecture—and to desultory lessons in Italian. I think he made me a better doctor; he certainly turned me into a better teacher.

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